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Applicants : John O'Connor et al.
Serial No. : 09/311,428 Examiner: L. Cook
Filed : May 13, 1999 Group Art Unit: 1641

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For METHODS FOR PREDICTING PREGNANCY OUTCOME IN
A SUBJECT BY hCG ASSAY



1185 Avenue of the Americas
New York, New York 10036
November 9, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the PTO-1449 form attached hereto as **Exhibit A**. Copies of references 4-17 are attached hereto as **Exhibits 1-14** respectively.

1. US Patent No. 4,514,505 issued April 30, 1985 to Canfield et al.;
2. US Patent No. 5,260,421 issued November 9, 1993 to Chappel et al.;
3. PCT International Application No. PCT/US99/02289, filed February 3, 1998, International Publication No. WO 99/41584, published August 19, 1999 on behalf of The Trustees of Columbia University in the City of New York;
4. Bogart et al., (1989) "Human Chorionic Gonadotropin Levels in Pregnancies with Aneuploid Fetuses", Prenat.Diagn. 9: 379-384 (**Exhibit 1**);

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5. Bogart et al., (1987) "Abnormal Maternal Serum Chorionic Gonadotropin Levels in Pregnancies with Fetal Chromosome Abnormalities", Prenat.Diagn. 7: 623-630 (**Exhibit 2**);
6. Cole et al., (1997) "Oligosaccharide Variants of hCG-related Molecules: Potential Screening Markers for Down Syndrome", Prenat.Diagn. 17: 1188-1190 (**Exhibit 3**);
7. Cole et al., (1998) "Hyperglycosylated hCG, A Potential Alternative To hCG in Down Syndrome Screening", Prenat.Diagn. 18: 926-933 (**Exhibit 4**);
8. Cole et al., (1997) "Urine β -Core Fragment, a Potential Screening Test for Ectopic Pregnancy and Spontaneous Abortion", Fetal.Diagn.Ther. 12: 336-339 (**Exhibit 5**);
9. Forest et al., (1995) "Screening for Down Syndrome During the First and Second Trimesters: Impact of Risk Estimation Parameters", Clin.Biochem. 28: 443-449 (**Exhibit 6**);
10. Kovalevskaya et al., (1999) "Early Pregnancy Human Chorionic Gonadotropin (hCG) Isoforms Measured By An Immunometric Assay For Choriocarcinoma-like hCG", J.Endocrinol. 161: 99-106 (**Exhibit 7**);
11. Spencer et al., (1996) "Urine Free beta-hCG and Beta Core in Pregnancies Affected by Down's Syndrome", Prenat.Diagn. 16: 605-613 (**Exhibit 8**);
12. Spencer et al., (1993) "Stability of Intact Chorionic Gonadotropin (hCG) in Serum, Liquid Whole Blood, and Dried

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- Whole-Blood Filter-Paper Spots: Impact on Screening for Down Syndrome by Measurement of Free β -hCG Subunit", Clin.Chem. 39: 1064-1068 (Exhibit 9);
13. Spencer et al., (1997) "Biochemical Markers of Trisomy 21 in Amniotic Fluid", Prenat.Diagn. 17: 31-37 (Exhibit 10);
 14. Valerio et al., (1996) "Maternal Serum Screening of Fetal Chromosomal Abnormalities by AFP, UE3, hCG and free- β hCG", Minerva.Ginecol. 48: 169-173 (Exhibit 11);
 15. Wald et al., (1994) "Four-Marker Serum Screening For Down's Syndrome", Prenat.Diagn. 14: 707-716 (Exhibit 12);
 16. Wald et al., (1994) "First Trimester Biochemical Screening for Down's Syndrome", Ann.Med. 26: 23-29 (Exhibit 13);
 17. Zimmermann et al., (1996) "Age-Independent Indices in Second-Trimester Serum Screening for Down's Syndrome Are Useless", Prenat.Diagn. 16: 79-82 (Exhibit 14);
 18. Birken et al., (1993) "Separation of Nicked Human Chorionic Gonadotropin (hCG), Intact hCG, and hCG Beta Fragment From Standard Reference Preparations and Raw Urine Samples", Endocrinology 133: 1390-1397;
 19. Birken et al., (1996) "Metabolism of hCG and hLH to Multiple Urinary Forms", Mol. Cell Endocrinol. 125: 121-131;
 20. Birken et al., (1996) "Isolation and Characterization of Human Pituitary Chorionic Gonadotropin", Endocrinology 137: 1402-1411;

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21. Cole et al., (1993) "The Deactivation of hCG by Nicking and Dissociation", J.Clin.Endocrinol.Metab. 76: 704-710;
22. Cole et al., (1985) "The Structures of the Serine-linked Sugar Chains on Human Chorionic Gonadotropin", Biochem.Biophys.Res.Comm. 126: 333-339;
23. Ellish et al., (1996) "A Prospective Study of Early Pregnancy Loss", Hum.Reprod. 11: 406-412;
24. Hoermann et al., (1994) "Immunological Recognition and Clinical Significance of Nicked Human Chorionic Gonadotropin in Testicular Cancer", Clin.Chem. 40: 2306-2312;
25. Kovalevskaya et al., (1995) "HLH Beta Core Fragment Immunoreactivity in the Urine of Ovulating Women: A Sensitive and Specific Immunometric Assay for its Detection", Endocrine 3: 881-887;
26. O'Connor et al., (1994) "Recent Advances in the Chemistry and Immunochemistry of Human Chorionic Gonadotropin: Impact on Clinical Measurements", Endocr.Rev. 15: 650-683;
27. O'Connor et al., (1998) "Differential Urinary Gonadotropin Profiles in Early Pregnancy and Early Pregnancy Loss", Prenat.Diagn. 18: 1232-1240;
28. O'Connor et al., (1988) "Development of Highly Sensitive Immunoassays to Measure Human Chorionic Gonadotropin, its Beta-subunit, and Beta Core Fragment in the Urine: Application to Malignancies", Cancer Res. 48: 1361-1366;
29. Wilcox et al., (1988) "Incidence of Early Loss of Pregnancy", N.Engl.J.Med. 319: 189-194;

30. Zinaman et al., (1996) "Estimates of Human Fertility and Pregnancy Loss", Fertil.Steril. 65: 503-509;
31. Acevedo et al., (1992) "Expression of Membrane-associated Human Chorionic Gonadotropin, Its Subunits, and Fragments by Cultured Human Cancer Cells", Cancer 69(7): 1829-1842;
32. Berger et al., (1993) "Variants of Human Chorionic Gonadotropin from Pregnant Women and Tumor Patients Recognized by Monoclonal Antibodies", J. Clin. Endocrinol. and Metabolism 77(2): 347-351;
- ✓ 33. Birken et al., (1999) "Development and Characterization of Antibodies to a Nicked and Hyperglycosylated Form of hCG from a Choriocarcinoma Patient", Endocrinology 10(2): 137-144;
34. Cole et al., (1991) "The Heterogeneity of Human Chorionic Gonadotropin (hCG). III. The Occurrence and Biological and Immunological Activities of Nicked hCG", Endocrinology 129(3): 1559-1567;
35. Hoermann et al., (1993) "Molecular Heterogeneity of Human Chorionic Gonadotropin in Serum and Urine from Patients with Trophoblastic Tumors", Clinical Investigation 71: 953-960;
36. Kovalevskaya et al., (1999) "Evaluation of Nicked Human Chorionic Gonadotropin Content in Clinical Specimens by a Specific Immunometric Assay", Clinical Chemistry 45(1):68-77;
37. Birken et al., (1993) "Separation of Nicked Human Chorionic Gonadotropin (hCG), Intact hCG, and hCG β Fragment from

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38. Ellish et al., (1996) "A Prospective Study of Early Pregnancy Loss", Human Reproduction 11(2): 407-408;
39. Hoermann et al., (1994) "Immunological Recognition and Clinical Significance of Nicked Human Chorionic Gonadotropin in Testicular Cancer" Clinical Chemistry 40(12): 2306-2312;
40. Knight, (1989) "The Carbohydrate Frontier", Biotechnology 7(1): 35 and 39-40;
41. O'Connor et al., (1988) "Development of Highly Sensitive Immunoassays to Measure Human Chorionic Gonadotropin, Its β -subunit, and Core Fragment in Urine: Application to Malignancies", Cancer Research 38: 1361-1366.

The subject application is a continuation-in-part of and claims the benefit under 35 U.S.C. §120 of PCT International Application No. PCT/US99/02289, filed February 3, 1999, which is a continuation-in-part of and claims the benefit under U.S.C. §120 of U.S. Serial No. 09/017,976, filed February 3, 1998.

The above listed references 18-30 were submitted to and considered by the United States Patent and Trademark Office in an Information Disclosure Statement filed on April 13, 1999, in connection with U.S. Serial No. 09/017,976, filed February 3, 1998. Above listed references 1, 2, and 37-41 were submitted to and considered by the United States Patent and Trademark Office in a Supplemental Information Disclosure Statement filed on August 18, 2000, in connection with U.S. Serial No. 09/017,976, filed February 3, 1998. Also, above listed references 3, and 31-

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36 are concurrently being submitted to the United States Patent and Trademark Office in a Supplemental Information Disclosure Statement filed on November 9, 2000, in connection with U.S. Serial No. 09/017,976, filed February 3, 1998. Accordingly, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office, since they were previously submitted to or cited by the United States Patent and Trademark Office in an application relied upon for an earlier filing date under 35 U.S.C. §120.

PCT International Application No. PCT/US99/02289, filed February 3, 1999, is a foreign counterpart application of the subject application. A Search Report was issued on September 13, 1999 in connection with PCT International Application No. PCT/US99/02289, filed February 3, 1999. A copy of the Search Report is attached hereto as **Exhibit B**. Above listed references 1, 2, and 37-41 were cited in the Search Report. As stated above, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office, since they were previously submitted to or cited by the United States Patent and Trademark Office in an application relied upon for an earlier filing date under 35 U.S.C. §120.

PCT International Application No. PCT/US00/13197, filed May 12, 2000, is a foreign counterpart application of the subject application. A Search Report was issued on August 11, 2000 in connection with PCT/US00/13197, filed May 12, 2000. A copy of the Search Report is attached hereto as **Exhibit C**. Above listed references 3, and 31-36 were cited in the Search Report. As stated above, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office, since they were previously submitted to or cited by the United States Patent and Trademark Office in an application relied upon for an earlier filing date under 35

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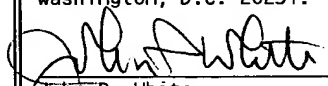
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the enclosed \$240.00 fee pursuant to 37 C.F.R. §1.17(p) for submission of an Information Disclosure Statement, is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

 11/9/00
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